29 Antihypertensive drug treatment and cardiovascular prevention: an update including the 2003–2004 secondary prevention trials

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KEYWORDS: blood pressure, clinical trial, heart failure, morbidity, mortality, myocardial infarction, prevention, stroke

ABSTRACT

In a meta-analysis published in June 2003, we reported that new and old classes of antihypertensive drugs had similar long-term efficacy and safety. To test whether our previous conclusions would hold, we updated our quantitative overview with new information from clinical trials published before 2005. To compare new and old antihypertensive drugs, we computed pooled odds ratios from stratified 2×2 contingency tables. Compared with old drugs (diuretics and β-blockers), calcium-channel blockers, angiotensin converting-enzyme inhibitors and AR1 blockers provided similar overall cardiovascular protection. However, the published results suggested that dihydropyridine calcium-channel blockers might offer a selective benefit in the prevention of stroke and inhibitors of the renin–angiotensin system in the prevention of heart failure. For prevention of myocardial infarction, the published results were more equivocal because of the benefit of amlodipine over placebo or valsartan in two trials, whereas other placebo-controlled trials of calcium-channel blockers or ACE inhibitors did not substantiate the expected benefit with regard to cardiac outcomes. In conclusion, the present results suggested that all antihypertensive drugs provide similar overall cardiovascular protection. To what extent within trial differences in blood pressure, rather than specific ancillary properties, might account for the observed outcome results in individual trials will be discussed in Chapter 30.

INTRODUCTION

Hypertension affects from 20% to 30% of the world's population and is a major cardiovascular risk factor [1,2]. The relation between cardiovascular risk and blood pressure is continuous, consistent across the age range, present in all

ethnic groups and independent of other risk factors [1,2]. The ultimate goal of any blood pressure lowering therapy is to reverse the risk associated with an elevated blood pressure and to prevent the cardiovascular complications associated with hypertension [3,4].

Placebo-controlled clinical trials proved that blood pressure lowering with various drug classes including diuretics, β–blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type-1 receptor (AR1) blockers reduces the incidence of cardiovascular complications. Over the past decade, clinical trials of blood pressure lowering drugs shifted focus from placebo-controlled to actively controlled designs in hypertensive patients and from primary to secondary prevention in high-risk patients with or without hypertension. The research goal underlying many of the more recent trials was to prove that the new classes of antihypertensive drugs provide superior protection against cardiovascular complications, especially in patients with a previous history of cardiovascular disease such as coronary heart disease or stroke. The aim of the present review was to summarize the main results of these studies in the light of the overall evidence from clinical trials in hypertension.

NEW VS. OLD ANTIHYPERTENSIVE DRUGS

In consecutive quantitative overviews of the actively controlled outcome trials [5–7], we computed pooled estimates for the comparison of new antihypertensive drugs, such as calcium-channel blockers, ACE inhibitors, AR1 blockers and α–blockers, with conventional therapy consisting of diuretics and/or β–blockers. In 2003 [7], we reviewed 18 reports on 15 trials [8–25], in which 1 20 574 patients had been randomized. Table 29.1 summarizes the characteristics of the trials comparing new antihypertensive drugs with conventional therapy, which were published in 2002 or later.

To compare new and old antihypertensive drugs, we computed pooled odds ratios from stratified 2×2 contingency tables. If Zelen's test of heterogeneity was significant, we used a random effects model.

Calcium-channel blockers vs. conventional therapy

For the comparison of calcium-channel blockers with conventional therapy, our last review [7] considered nine trials [8,10–13,19–21,26] with 67 435 randomized patients. These trials were ALLHAT/Aml [21], CONVINCE [19], ELSA [20,22], INSIGHT [12], MIDAS [8], NICS [10], NORDIL [13], STOP2/CCBs [11] and VHAS [26]. For none of the outcomes considered in these analyses, including total and cardiovascular mortality, all cardiovascular events (Fig.29.1), stroke (Fig. 29.2), myocardial infarction (Fig. 29.3) or heart failure, heterogeneity among the trials reached statistical significance [7].

The pooled odds ratios expressing possible benefit of calcium-channel blockers over old drugs were close to unity and nonsignificant for total mortality (0.98; 95% confidence interval (CI), 0.92–1.03; $P = 0.42$), cardiovascular mortality (1.03; CI, 0.95–1.11; $P = 0.51$), all cardiovascular events (1.03; CI, 0.99–1.08; $P = 0.15$) and myocardial infarction (1.02; CI, 0.95–1.10; $P = 0.61$). Calcium-channel blockers provided slightly better protection against fatal and nonfatal stroke than old drugs (Fig.29.2). For the nine trials combined [8,10–12,20,21,26–28], the

Table 29.1 Trials of new vs. old drug classes published in 2002–2004

	ALLHAT/Aml	ALLHAT/Lis	ANBP2	CONVINCE	ELSA	HYVET/AD	INVEST	SCOPE	SHELL
Reference(s)	[21]	[21]	[23]	[19]	[20,22]	[25]	[29]	[24,122]	[30]
Degree of blinding	Double	Double	PROBE	Double	Double	PROBE	PROBE	Double	PROBE
Number of patients	24 303	24 309	6083	16 476	2334	857	22 576	4 937	1882
Reference (old drugs)	15 255	15 255	3039	8 297	1157	426	11 267	2 460	940
Experimental (new drugs)	9 048	9 054	3044	8 179	1177	431	11 309	2 477	942
Treatment									
Old drug(s)	Chlorthalidone	Chlorthalidone	Diuretics	Atenolol or HCTZ	Atenolol	BFMT or other thiazide	Atenolol	Placebo plus AH drugs[a]	Chlorthalidone
New drug(s)	Amlodipine	Lisinopril	ACEIs	COER-verapamil	Lacidipine	ACEIs	Verapamil	Candesartan	Lacidipine
Primary endpoint	CM+MI	CM+MI	ACM+CVE	CVM+S+MI	Rate of CIMT	ACM+S	ACM+S+MI	CVM+MI+S	CVE
Mean age (years)	66.9	66.9	72.0	65.6	56.0	83.8	52.1	76.4	72.3
Mean systolic/ diastolic BP (mmHg)									
At randomization	146/84[b]	146/84[b]	167/91	150/87[b]	164/101	181/100	151/87[b]	166/90[b]	178/87
Difference during follow-up[c]	–1.1[d]/+0.6[d]	–2.3[d]/+0.2	–1.4[d]/~0	+0.1/+0.7	+0.6/+0.2	+1.4/~0	–0.2/–0.3	+3.2[d]/+1.6[d]	+1.7/–0.3
Mean serum creatinine (mmol/l)	78	78	...	...	84	102	...	88	...
Proportion of patients (%)									
Women	47.1	46.7	49.0	55.4	45.2	63.5	52.1	64.5	61.3
AH drug treatment before entry	90.2	90.2	62.0	83.5	63.3	47.5	86.6	52.7	51.8

Table 29.1
Continued

	ALLHAT/Aml	ALLHAT/Lis	ANBP2	CONVINCE	ELSA	HYVET/AD	INVEST	SCOPE	SHELL
History of CV complications[e]	36.1	36.4	15.0	12.3	2.4	6.9	100.0 (CAD)	8.4	30.6
Left ventricular hypertrophy	21.0	20.7	...	12.3	...	...	21.9	...	...
Diabetes mellitus	36.4	36.0	7.0	19.8	7.4[f]	...	28.3	12.1	13.2
Mean or median follow-up (years)	4.9	4.9	4.1	3.0	3.7	1.1	2.7	3.7	2.7

[a]88% of the SCOPE patients [24] allocated placebo were on open-label antihypertensive therapy, mainly with diuretics (62%) or β–blockers (26%).
[b]Blood pressure at entry was measured on antihypertensive medication in previously treated patients.
[c]Negative values indicate tighter blood pressure control on old drug classes.
[d]Significant difference in achieved blood pressure between randomized groups.
[e]History of myocardial infarction, stroke excluding transient ischemic attack, or surgical or percutaneous revascularization.
[f]Fasting blood glucose concentration > 126 mg/dl[22].
Note: ACEI = angiotensin converting-enzyme inhibitor; ACM = all-cause mortality; AH = antihypertensive; BFMT = bendroflumethiazide; CAD = documented coronary heart disease; COER = controlled onset-extended release; CM = coronary mortality; CVE = cardiovascular events; CIMT = carotid intima–media thickening; CVM = cardiovascular mortality; HCTZ = hydrochlorothiazide; MI = nonfatal myocardial infarction; PROBE = prospective randomized open blinded endpoint study; S = nonfatal stroke. Acronyms of trials are explained in a separate section of this article.

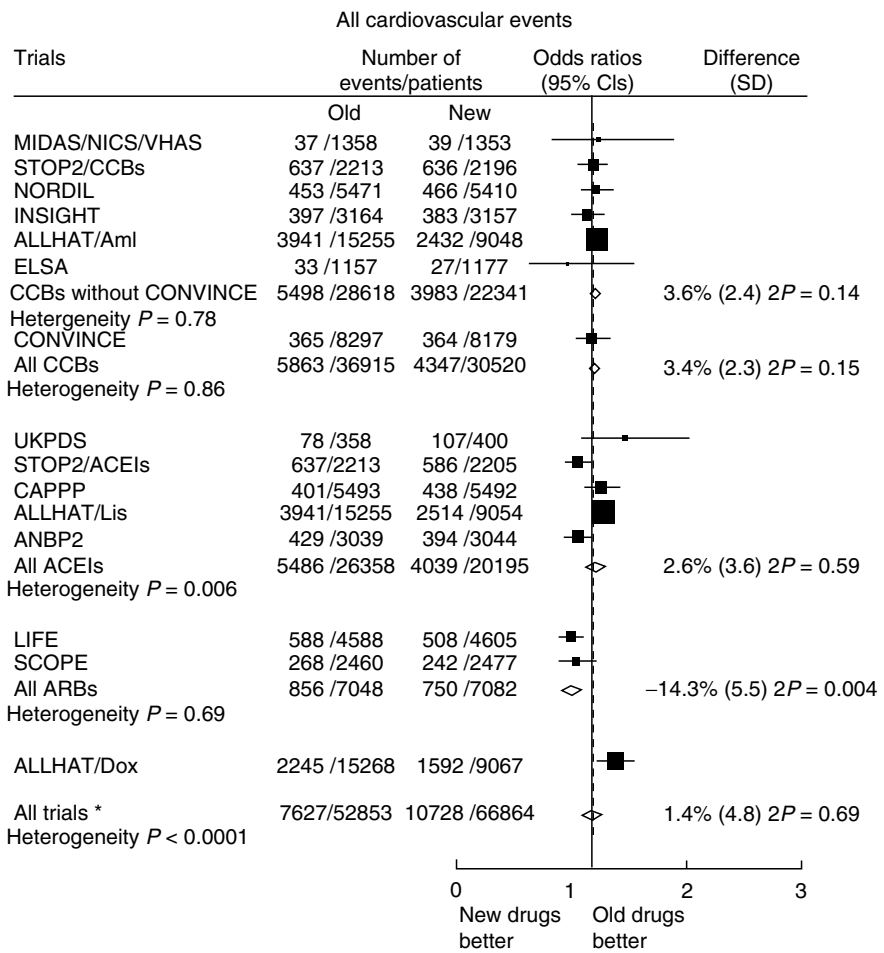

Fig. 29.1 Effects of antihypertensive treatment on all cardiovascular events in trials comparing new with old antihypertensive drugs. Asterisks indicate significant heterogeneity and pooled estimates calculated from a random effects model. Solid squares represent the odds ratios in trials and have a size proportional to the number of events. The 95% confidence intervals for individual trials are denoted by lines and those for pooled odds ratios by diamonds. Acronyms of trials are explained in a separate section of this article. Reproduced with permission from Ref. [7]. For update, including SHELL [30] and INVEST [29], see section new vs. old antihypertensive drugs.

pooled odds ratio for stroke was 0.92 (CI, 0.84–1.01; $P = 0.07$). After exclusion of CONVINCE [28], a large trial based on verapamil, the odds ratio for stroke was 0.90 and reached significance (CI, 0.82–0.98; $P = 0.02$). For heart failure, calcium-channel blockers provided less protection than conventional therapy, regardless of whether (1.33; CI, 1.22–1.44; $P < 0.0001$) or not (1.33; CI, 1.22–1.46; $P < 0.0001$), we incorporated the CONVINCE trial [28] in the pooled estimates.

A rerun of the analysis in December 2004 with coronary heart disease and stroke as the outcomes of interest confirmed the above results [7]. In addition to the nine trials [8,10–12,20,21,26–28] previously reviewed, we also included INVEST [29] and SHELL [30], but not AASK because published information on cause-specific cardiovascular complications was not enough detailed [31]. The *P*-values for heterogeneity remained nonsignificant. Pooled estimates were 1.02

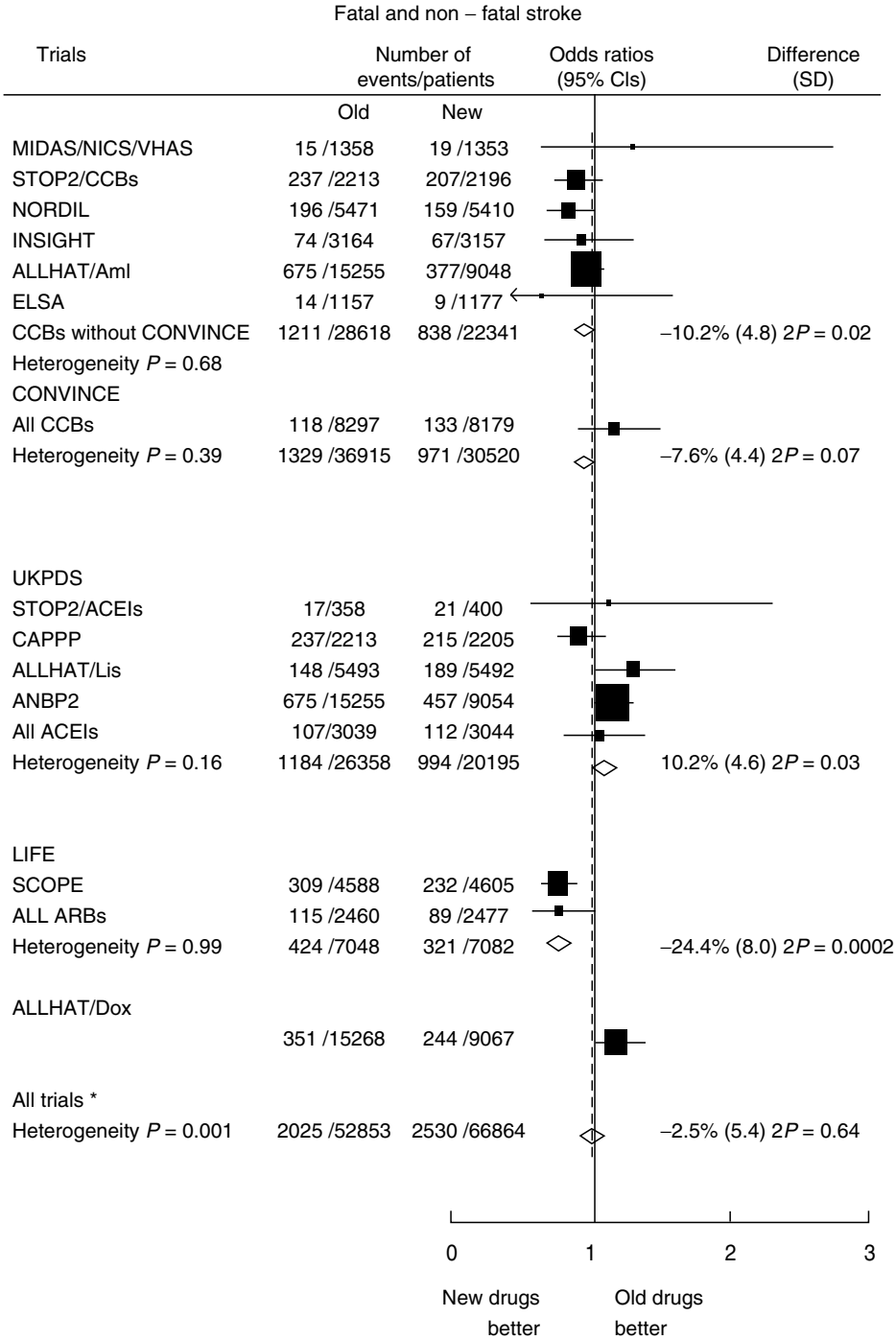

Fig. 29.2 Effects of antihypertensive treatment on fatal and nonfatal stroke in trials comparing new with old antihypertensive drugs. The asterisk indicates significant heterogeneity and pooled estimates calculated from a random effects model.
For further explanation see Fig. 29.1. Reproduced with permission from Ref. [7]. For update, including SHELL [30] and INVEST [29], see section new vs. old antihypertensive drugs.

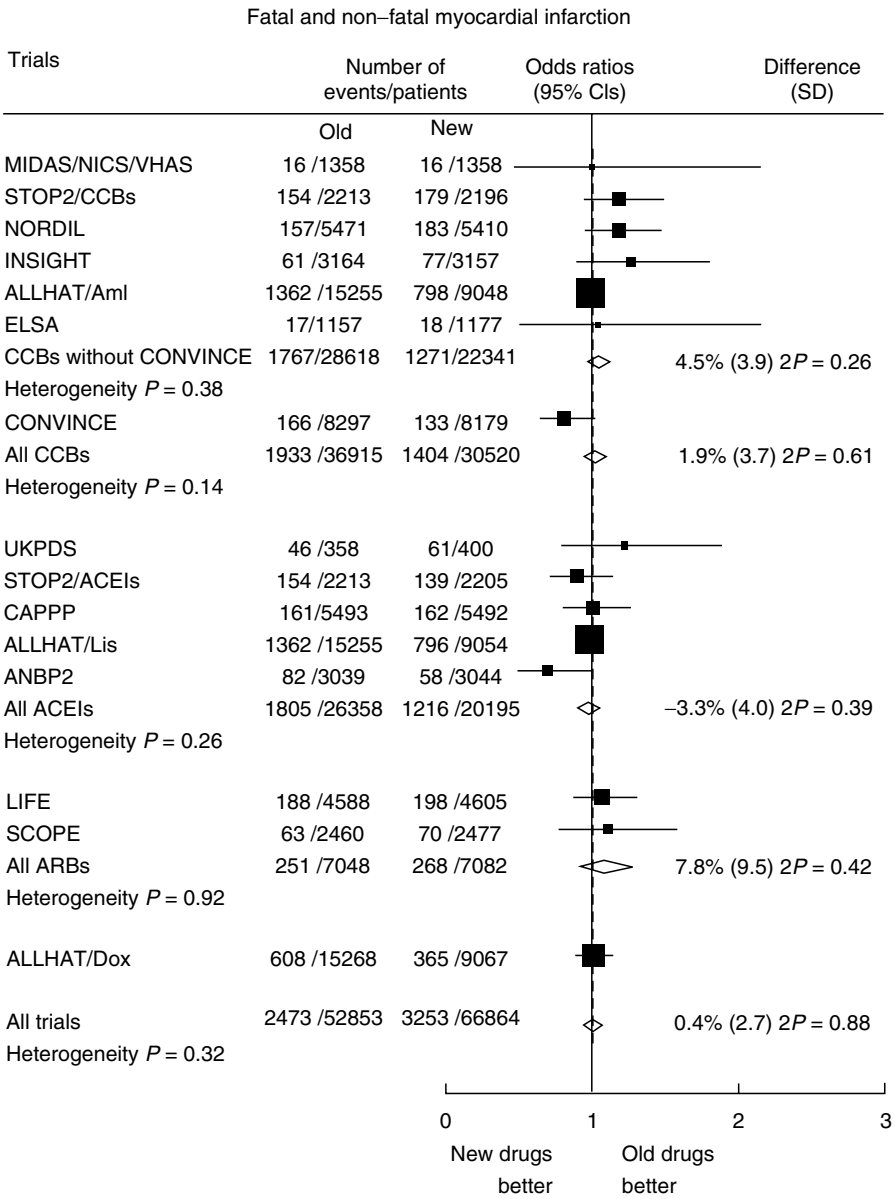

Fig. 29.3 Effects of antihypertensive treatment on fatal and nonfatal myocardial infarction in trials comparing new with old antihypertensive drugs. For further explanation see Fig. 29.1. Reproduced with permission from Ref. [7]. For update, including SHELL [30] and INVEST [29], see section new vs. old antihypertensive drugs.

(CI, 0.96–1.09; $P = 0.55$) and 0.92 (CI, 0.85–0.99; $P = 0.03$) for coronary heart disease and stroke, respectively. After exclusion of the two verapamil-based trials [28,29], the common odds ratio for stroke was 0.90 (CI, 0.82–0.98; $P = 0.02$).

ACE inhibitors vs. conventional therapy

Our 2003 review [7] considered six trials [9,11,16,21,23,25] with 47 519 randomized patients, which compared ACE inhibitors with old drugs. These trials

included: ALLHAT/Lis [21], ANBP2 [23], CAPPP [9], HYVET/AD [25], STOP2/ACEIs [11] and UKPDS/CA [16]. For total and cardiovascular mortality, stroke (Fig.29.2) and myocardial infarction (Fig.29.3), *P*-values indicating heterogeneity among these trials were nonsignificant. In contrast, for all cardiovascular events (Fig.29.1) and heart failure heterogeneity was significant due to the ALLHAT findings [21]. Compared to chlorthalidone [21], the ALLHAT patients allocated lisinopril had greater risks of stroke (1.15; CI, 1.02–1.30; $P = 0.02$), heart failure (1.19; CI, 1.07–1.31; $P < 0.001$), and hence combined cardiovascular disease (1.10; CI, 1.05–1.16; $P < 0.001$).

The pooled odds ratios expressing possible benefit of ACE inhibitors over conventional therapy were close to unity and nonsignificant for total mortality (1.00; CI, 0.94–1.06; $P = 0.89$), cardiovascular mortality (1.02; CI, 0.94–1.11; $P = 0.61$), all cardiovascular events (1.03; CI, 0.94–1.12; $P = 0.59$), myocardial infarction (0.97; CI, 0.90–1.04; $P = 0.39$) and heart failure (1.04; CI, 0.89–1.22; $P = 0.64$). Compared to old drugs, ACE inhibitors gave slightly less protection against stroke with a pooled odds ratio of 1.10 (CI, 1.01–1.20; $P = 0.03$). A further review of the literature in December 2004 did not reveal new trials comparing ACE inhibitors to diuretics in addition to the six studies already analyzed in 2003 [7]. The AASK trial [31] incorporated a comparison of ramipril with metoprolol, but only provided aggregate cardiovascular outcomes and could therefore not be included.

AR1 blockers vs. conventional therapy

The LIFE trial (Table 29.2) tested losartan vs. atenolol as first-line treatment in hypertensive patients with left ventricular hypertrophy [17,18]. SCOPE [24] was set up as a double-blind placebo-controlled trial. However, open-label antihypertensive drugs, which mainly consisted of diuretics, β–blockers or both classes of old drugs, were added to the double-blind study medication in a considerably greater proportion of the patients randomized to placebo than in those allocated candesartan. There was no statistical heterogeneity between the results of these two trials [7]. Compared to control, treatment initiated with an AR1 blocker provided similar protection against total mortality, cardiovascular death and myocardial infarction. The pooled odds ratios were 0.91 (CI, 1.81–1.02; $P = 0.09$), 0.89 (CI, 0.77–1.04; $P = 0.15$) and 1.08 (CI, 0.90–1.29; $P = 0.42$), respectively. The corresponding estimates for stroke and all cardiovascular events were 0.77 (CI, 0.65–0.88; $P = 0.0002$) and 0.86 (CI, 0.77–0.95; $P = 0.004$), respectively.

New drugs vs. old antihypertensive drugs

Our 2003 review demonstrated that across 15 trials [8–21,23–25] outcomes for total and cardiovascular mortalityas well as for myocardial infarction (Fig. 29.3) were consistent. The pooled odds ratios did not deviate from unity, averaging 0.98 (CI, 0.94–1.02; $P = 0.38$), 1.00 (CI, 0.95–1.07; $P = 0.88$) and 1.00 (CI, 0.95–1.06; $P = 0.87$), respectively. In contrast, for all cardiovascular events (Fig. 29.1), stroke (Fig. 29.2) and heart failure, there was significant heterogeneity ($P < 0.001$) across the 15 trials [8–21,23–25], which was largely due to the ALLHAT results [14,21,32]. First-line therapy with a diuretic provided less benefit than amlodipine and doxazosin with regard to heart failure than lisinopril and doxazosin in

Table 29.2 Secondary prevention trials of dihydropyridine calcium-channel blockers and AR1 blockers

	LIFE	VALUE	ACTION	CAMELOT/Aml	IDNT2	NICOLE	PREVENT
Reference(s)	[17,18]	[39,40]	[44]	[41]	[33,35]	[46,47]	[42,43]
Degree of blinding	Double	Double	Double	Double	Double	Double	Double
Number of patients	9193	15 245	7665	1318	1715	819	825
Reference	4588	7 596	3840	655	569	411	408
Calcium-channel/AR1 blocker	4605	7 649	3825	663	1146	408	417
Treatment							
Reference	Atenolol	Amlodipine	Placebo	Placebo	Placebo	Placebo	Placebo
Calcium-channel/AR1 blocker	Losartan	Valsartan	Nifedipine GITS	Amlodipine	Amlodipine or Irbesartan	Nisoldipine	Amlodipine
Primary endpoint	CVM+MI+S	MI+HF	ACM+MI+A+ HF+S+PR[a]	CVM+MI+ CAR+ A+CR+HF+ S+PAD	ACM+ESRD+ SCrt(2×)	Rate of COA	Rate of CAA
Mean age (years)	66.9	67.2	63.5	57.3	58.9	60.3	56.9
Mean systolic/diastolic BP (mmHg)[b]							
At randomization		155/88	137/80	129/78	159/87	129/78	129/79
Difference during follow-up[c]	+1.1[d]/–0.2	–2.2[d]/–1.6[d]	+6.0[d]/+3.0[d]	+4.8[d]/+3.0[d]	+5.0[d]/+3.0[d,e]§	+9.1[d]/+3.3[d]	+6.8[d]/+3.7[d]
Proportion of patients (%)							
Women	54.0	42.4	20.6	25.4	33.5	20.0	19.9
Hypertension at entry	100.0	100.0	51.9	60.8	100.0[f]	40.6	...
History of CHD (MI)	16.0 (…)[g]	45.8 (...)	100.0 (50.9)	100.0 (37.6)	16.5 (...)	100.0 (42.5)	100.0 (44.9)
History of stroke	7.9&	19.8[h]	...	3.9	11.6	...	3.0
Diabetes mellitus	13.0	31.7	14.5	18.6	100.0	10.4	0[i]
Concomitant therapy (%)							
Lipid-lowering drugs	...	46.4	68.5	83.7	...	41.0	27.3

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Table 29.2
Continued

	LIFE	VALUE	ACTION	CAMELOT/AmI	IDNT2	NICOLE	PREVENT
Antiplatelet agents	...	72.6	86.0	94.9	...	...	...
Mean or median follow-up (years)	4.8	4.2	4.9	2.0	2.6	3.0	3.0

[a]Primary endpoint for efficacy.
[b]Blood pressure at entry was always measured on antihypertensive medication in previously treated patients.
[c]Negative values indicate tighter blood pressure control in the reference group.
[d]Significant difference in achieved blood pressure between randomised groups.
[e]The blood pressure differences between the amlodipine and irbesartan groups were nonsignificant.
[f]Hypertension is a blood pressure ≥ 135 mmHg systolic or ≥ 85 mmHg diastolic or use of antihypertensive medications.
[g]In LIFE, all patients had electrocardiographic left ventricular hypertrophy.
[h]Stroke includes transient ischemic attack.
[i]Fasting blood glucose concentration ≥ 200 mg/dL [43]
Note: A = refractory or hospitalized angina pectoris; ACM = all-cause mortality; CAA = atheromatosis of the carotid artery; COA = coronary atheromatosis; CAR = resuscitated cardiac arrest; CHD = coronary heart disease; CR = coronary revascularization; CVM = cardiovascular mortality; ESRD = end-stage renal disease; HF = heart failure; MI = nonfatal myocardial infarction; PAD = peripheral arterial disease; PR = peripheral revascularization; S = nonfatal stroke; SCrt(2×) = doubling of the serum creatinine concentration. Acronyms of trials are explained in a separate section of this article.

the prevention of stroke. For all cardiovascular events and stroke the overall odds ratios were 1.01 (CI, 0.95–1.09; $P = 0.69$) and 0.98 (CI, 0.88–1.08; $P = 0.64$), respectively. Compared to conventional therapy, new drugs offered less protection against heart failure with a pooled odds ratio of 1.23 (CI, 1.03–1.47; $P = 0.02$).

CALCIUM-CHANNEL BLOCKERS VS. AR1 BLOCKERS

Two secondary prevention trials (Table 29.2), IDNT2 [33–35] and VALUE [36–40], allowed a direct comparison between a dihydropyridine calcium-channel blocker and an AR1 blocker.

In the IDNT2 trial [33], 1715 hypertensive patients with nephropathy due to type-2 diabetes were randomized to placebo, irbesartan (300 mg/day) or amlodipine (10 mg/day). The primary endpoint was a composite of a doubling of the baseline serum creatinine concentration, the development of end-stage renal disease or death from any cause. The adjusted relative risk of the primary endpoint was 0.81 (CI, 0.67–0.99; $P = 0.03$) for irbesartan vs. placebo and 0.76 (CI, 0.63–0.92; $P = 0.005$) for irbesartan vs. amlodipine with no difference between amlodipine and placebo 1.07 (CI, 0.89–1.29; $P = 0.47$). Doubling of the serum concentration of creatinine mainly underlay these results because the between-group differences in the other constituents of the composite endpoint were not statistically significant [33]. The incidence of cardiovascular events was similar among the three groups. However, among the components of the composite cardiovascular outcome, there was a trend toward a decrease in strokes in patients receiving amlodipine vs. those randomized to placebo (hazard ratio, 0.62; CI, 0.35–1.22; $P = 0.18$). Likewise, patients receiving amlodipine had a significantly lower rate of myocardial infarction when compared to placebo recipients (0.58; CI, 0.37–0.92; $P = 0.02$). In contrast, patients receiving irbesartan experienced a lower incidence of heart failure than the placebo group (0.72; CI, 0.52–1.00; $P = 0.048$) or the patients randomized to amlodipine (0.65; CI, 0.48–0.87; $P = 0.004$).

The VALUE investigators undertook a double-blind clinical trial to test the hypothesis that, for the same degree of blood pressure lowering, inhibition of the renin system at the level of the AR1 would be more effective in the prevention of cardiac morbidity and mortality than calcium-channel blockade [36–40]. Across 943 centers and 31 countries [36,37,39], 15 245 high-risk patients were randomized to antihypertensive treatment based on either valsartan (80–160 mg/day) or amlodipine (5–10 mg/day) and followed-up for a median of 4.2 years. The VALUE investigators assumed that the primary endpoint, a composite of fatal and nonfatal cardiac endpoints, would run at a rate of 25 events per 1000 patient-years [37]. Within less than 5 years, the number of cardiac endpoints exceeded the projected number of 1450 by 149. Cardiac endpoints occurred at similar rates in the two treatment groups because the incidence of myocardial infarction was lower (0.84; CI, 0.72–0.98; $P = 0.02$) on amlodipine than valsartan, whereas on amlodipine the risk of heart failure tended to be increased (1.12; CI, 0.97–1.30; $P = 0.12$). The incidence of fatal and nonfatal stroke was lower (0.87; CI, 0.74–1.02; $P = 0.08$) on amlodipine than valsartan. A unique feature of VALUE was the comprehensive assessment of cardiovascular risk at baseline [37] and the implementation of a strategy to stabilize risk at a high level across six strata based on gender and age (50–59, 60–69 and ≥ 70 years).

PLACEBO-CONTROLLED SECONDARY PREVENTION TRIALS

Several secondary prevention trials addressed the question whether new antihypertensive agents given on top of usual therapy, compared to usual antihypertensive therapy, provided superior cardiovascular protection. In five trials with 12 342 randomized patients (Table 29.2) the experimental agent was a dihydropyridine calcium-channel blocker: amlodipine in CAMELOT/Aml [41], PREVENT [42.43] and IDNT2 [33–35]; nifedipine GITS (gastrointestinal therapeutic system) in ACTION [44,45]; and nisoldipine in NICOLE [46,47]. In nine trials with 43 227 randomized patients (Table 29.3), the investigational drug was an ACE inhibitor: enalapril in CAMELOT/En [41] and SCAT [48]; perindopril alone in EUROPA [49] and PROGRESS/Per [50,51] or in combination with indapamide in PROGRESS/Com [50,51]; ramipril in DIABHYCAR [52–54], HOPE [55,56] and PART2 [57]; and trandolapril in PEACE [58]. All patients randomized in these trials were high-risk patients with a history of cardiovascular disease and/or diabetes mellitus [54–56], nephropathy [33,35], documented coronary heart disease [41,43,44,46–49,57,58] or a previous cerebrovascular accident [51,59].

All [33,41,44,49,54,55,58], but five [43,46,48,51,57], placebo-controlled secondary prevention trials had a composite primary endpoint (Tables 29.2 and 29.3). In three trials [41] the composite endpoint included coronary [41,58] or peripheral [44] revascularization procedures. In four trials the primary endpoint consisted only of the rate of change of carotid [43,48] or coronary [46,57] atherosclerosis and hard endpoints, such as stroke or myocardial infarction were only secondary outcomes. The use of composite endpoints with varying definitions (Tables 29.2 and 29.3) and the wide range of secondary endpoints made obtaining pooled estimates for overall treatment effects difficult. CAMELOT [41] and PEACE [58] only reported nonfatal cases of myocardial infarction. Stroke included transient ischemic attack in CAMELOT [41] and was limited to nonfatal events in PART2 [57].

Among the five trials of dihydropyridine calcium-channel blockers [35,41,43,44,47], there was no heterogeneity in the results with regard to the composite of all cardiovascular events including procedures and revascularization ($P = 0.52$), stroke ($P = 0.81$) and myocardial infarction ($P = 0.16$). The pooled odds ratios were: 0.78 (CI, 0.72–0.85; $P < 0.0001$), 0.71 (CI, 0.55–0.92; $P = 0.0015$) and 0.97 (CI, 0.83–1.13; $P = 70$), respectively. When the analysis was limited to the three trials involving amlodipine as the experimental agent [35,41,43], these pooled estimates were: 0.73 (CI, 0.62–0.85; $P = 0.0001$) for cardiovascular events; 0.60 (CI, 0.36–0.97; $P = 0.038$) for stroke; and 0.69 (CI, 0.49–0.97; $P = 0.033$) for myocardial infarction.

Among the placebo-controlled trials of ACE inhibitors [41,48,49,51,54,55,57,58], there was significant heterogeneity ($P \leq 0.001$) in the outcome results for all cardiovascular endpoints and stroke, but not for myocardial infarction ($P = 0.25$). Cardiovascular events included revascularization procedures in CAMELOT [41] and total mortality in SCAT [48], but not in the other trials [49,51,54,55,57,58]. Across the available studies [41,48,49,51,54,55,57,58], the pooled odds ratios for ACE inhibition vs. placebo were highly significant ($P < 0.0001$), amounting to 0.81 (CI, 0.77–0.86) for cardiovascular events, 0.77 (CI, 0.69–0.84) for stroke and 0.80 (CI, 0.73–0.86) for myocardial infarction. In sensitivity analyses, we excluded EUROPA [49] and PROGRESS/Per [51], two trials of perindopril given in monotherapy and

Table 29.3 Placebo-controlled trials of ACE inhibitors for secondary prevention

	CAMELOT/En	DIABHYCAR	EUROPA	HOPE	PART2	PEACE	PROGRESS/ Per	PROGRESS/ Com	SCAT
Reference(s)	[41]	[52,54]	[49]	[55,56]	[57]	[58]	[51,59]	[51,59]	[48]
Degree of blinding	Double	Double	Double	Double	Double	Double	Double	Double	Double
Number of patients	1328	4912	12 218	9297	617	8290	2561	3544	460
Reference	655	2469	6 108	4652	309	4132	1280	1774	231
ACE inhibitor	673	2443	6 110	4645	308	4158	1281	1770	229
Treatment									
Reference	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
ACE inhibitor	Enalapril	Ramipril	Perindopril	Ramipril	Ramipril	Trandolapril	Perindopril	Perindopril + Indapamide	Enalapril
Primary endpoint	CVM+MI+CAR + A+CR+HF+ S+PAD	CVM+MI+S+ HF+ESRD	CVM+MI+ CAR	CVM+MI+S	Rate of COA	CVM+MI+CR	S	S	Rate of CAA
Mean age (years)	57.9	65.1	60.0	66.0	60.5	64.0	65.0	63.0	61.0
Mean systolic/ diastolic BP (mmHg)									
At randomization	129/77	145/82	137/82	139/79	133/79	133/78	144/84	149/87	130/78
Difference during follow-up[a]	+5.6[b]/+3.4[b]	+1.5[b]/+0.3	+5.0[b]/+2.0[b]	+3.0[b]/+1.0[b]	+5.0[b]/4.0[b]	+2.0[b]/1.2[b]	+4.9[b]/+2.8[b]	+12.3[b]/+5.0[b]	+4.0[b]/+2.0[b]
Proportion of patients (%)									
Women	27.6	30.1	14.6	26.7	18.0	18.0	31.6	29.4	10.9
Hypertension at entry	60.0	55.7	27.1[c]	46.8	...	45.5	39.6	53.7	35.2
History of CHD (MI)	100.0 (39.0)	... (6.0)	100.0 (64.7)	81.0 (52.6)	68.0 (42.0)	100.0 (55.0)	13.5 (...)	17.9 (...)	100.0 (70.4)

Table 29.3
continued

	CAMELOT/En	DIABHYCAR	EUROPA	HOPE	PART2	PEACE	PROGRESS/ Per	PROGRESS/ Com	SCAT
History of stroke	4.3	4.2	3.5[d]	10.9[d]	10.0[d]	6.5	100.0[d]	100.0[d]	...
Diabetes mellitus	18.7	100.0	12.3	38.5	8.5	17.0	13.2	12.0	10.9
Concomitant therapy (%)									
Lipid-lowering drugs	83.0[e]	28.5	63.0[e]	28.5	29.5	70.0	15.0	15.0	~50.0[f]
Antiplatelet agents	95.0[e]	18.7	91.0[e]	76.1	81.0	90.5	77.0	77.0	89.9
Mean or median follow-up (years)	2.0	3.9	4.2	5.0	4.0	4.8	4.0	4.0	4.0

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Blood pressure at entry was always measured on antihypertensive medication in previously treated patients.
[a]Negative values indicate tighter blood pressure control on old drug classes.
[b]Significant difference in achieved blood pressure between randomised groups.
[c]Hypertension is a blood pressure ≥ 160 mmHg systolic, ≥ 90 mmHg diastolic (PROGRESS) or ≥ 95 mmHg diastolic (EUROPA), or use of antihypertensive medications.
[d]Stroke includes transient ischemic attack or amaurosis fugax.
[e]Concomitant therapy not only recorded at baseline, but also during follow-up.
[f]In a factorial design, the patients were also randomized to simvastatin or placebo.
Note: A = refractory or hospitalized angina pectoris; CAA = atheromatosis of the carotid artery; COA = coronary atheromatosis; CAR = resuscitated cardiac arrest; CHD = coronary heart disease; CR = coronary revascularization; CVM = cardiovascular mortality; ESRD = end-stage renal disease; HF = heart failure; MI = nonfatal myocardial infarction; PAD = peripheral arterial disease; S = nonfatal stroke. Acronyms of trials are explained in a separate section of this article.

DIABHYCAR [54], in which the difference in systolic pressure between the ramipril and placebo group was only 1.5 mmHg. These exclusions removed the heterogeneity for stroke ($P = 0.11$) and decreased the common odds ratio for stroke to 0.63 (CI, 0.56–0.72; $P < 0.0001$).

In addition to the endpoints reviewed above, several secondary prevention trials, including AASK [31,60], ABCD [61–65], BENEDICT [66,67], CALM [68], HOPE [56], IRMA2 [69], REIN [70], RENAAL [71], IDNT2 [33–35] and a number of earlier published smaller trials [72] demonstrated that ACE inhibitors, AR1 blockers or their combination reduce the progression of renal impairment in patients with microalbuminuria or proteinuria, associated or not with diabetes mellitus.

INTERPRETATION OF THE EVIDENCE

This updated overview confirmed that old and new antihypertensive drugs provide similar overall cardiovascular protection. The evidence suggested that dihydropyridine calcium-channel blockers might offer a slight but selective benefit in the prevention of stroke and inhibitors of the renin–angiotensin system in the prevention of heart failure. For prevention of myocardial infarction, the published results were more equivocal because of the benefit of amlodipine over placebo [35] or valsartan [39,40] in two trials, whereas other placebo-controlled trials of calcium-channel blockers [44,47] or ACE inhibitors [41,54,58] did not substantiate the expected advantage with regard to cardiac outcomes.

Prevention of stroke

In 2001 [5], we already noticed that calcium-channel blockers, compared to conventional therapy with diuretics and/or β–blockers, gave 13.5% ($P = 0.03$) more reduction in the risk of stroke. In our 2003 review [7], we additionally included ALLHAT/Aml [21], CONVINCE [19] and ELSA [20,22] and in our present overview also INVEST [29] and SHELL [30]. The number of randomized patients thereby increased from 23 454 in 2001 [5] to 67 435 in 2003 [5] and 91 893 currently. With these additional patients, the overall estimates of benefit of calcium-channel blockers over old drugs in the prevention of stroke were 7.6% ($P = 0.07$) in 2003 [5] and presently 8.0% ($P = 0.03$). These findings were in line with those of consecutive overviews published by the Blood Pressure Lowering Treatment Trialists' Collaboration [73–75]. In 2000 [74], starting from individual patient records and summary tabular data [73], this consortium reviewed five trials, including INSIGHT [12], NICS [10], NORDIL [13], STOP2/CCBs [11] and VHAS [26]. Their 2003 update [75] additionally considered AASK [31,60,76,77], ALLHAT/Aml [21], CONVINCE [19], ELSA [20,22], but not INVEST [29]. In these consecutive overviews, the estimates of benefit of calcium-channel blockers over old drugs in the prevention of stroke were 13.0% [74] and 7.0% [75], respectively. All calcium-channel blockers bind to a specific receptor domain situated on the α_1-subunit of the L-type calcium channel [78], but amlodipine also binds to diltiazem receptors [78]. These pharmacologic characteristics, but more importantly, the low probability of heterogeneity among the trials involving dihydropyridines and diltiazem ($P = 0.80$) provided a rationale for a sensitivity analysis combining these two subclasses of calcium-channel blockers. After exclusion of

the two verapamil-based trials [28,29], we found a 10.0% (P = 0.02) better prevention of stroke on calcium-channel blockers than old drugs.

In 2001 [5], we reviewed three trials comparing ACE inhibitors to conventional therapy [9,11,16], which included 16 551 randomized patients. Both treatment modalities gave similar protection against cerebrovascular accidents [5]. In the present analysis, the number of relevant trials increased to five [9,11,16,21,23] and the number of randomized patients rose to 46 553. In contrast to our former conclusions [5], ACE inhibitors gave 10.2% less reduction in the risk of stroke than the old antihypertensive drugs. These results are in line with the secondary prevention trials in patients with a history of cerebrovascular disease, which tested inhibitors of the renin system [51,79] or indapamide [80] against placebo. Neither atenolol in TEST [79] nor perindopril in the monotherapy arm of the PROGRESS trial [51] reduced the incidence of stroke recurrence, whereas in the Chinese PATS trial [80] for a similar reduction in systolic blood pressure (5.0 mmHg) indapamide decreased recurrent stroke by 29%. In the EUROPA trial [49], in patients with coronary heart disease, perindopril given on top of usual therapy did no better than placebo in the primary prevention of stroke.

In two trials [23,24], AR1 blockers resulted in 24.4% better stroke prevention than did the old drugs, whereas the opposite trend was observed in the doxazosin arm of the ALLHAT trial (–17.5%, P = 0.04). A comprehensive overview of observational cohort studies recently highlighted that throughout middle and old age blood pressure is strongly and directly related to stroke mortality [1]. Hypertension is the most consistent and powerful predictor of stroke [1,81] and is involved in nearly 70% of strokes [81]. It is therefore impossible to interpret the stroke results of our overview without taking into account the within-trial differences in achieved systolic blood pressure (see Chapter 30).

Prevention of myocardial infarction

We reported in 2001 [5,6] that calcium-channel blockers, compared to diuretics and β–blockers, gave 19.2% less reduction of the risk of myocardial infarction [5]. The corresponding pooled estimate reported by the Blood Pressure Lowering Treatment Trialists' Collaboration was 12.0% [74]. In the present update, the shortfall of calcium-channel blockers relative to conventional therapy disappeared in part as a result of the positive trend in favor of verapamil in CONVINCE (0.81; CI, 0.64–1.02; P = 0.08 [28]) and the similar coronary outcomes on amlodipine and chlorthalidone in ALLHAT (0.99; CI, 0.90–1.08; P = 0.79 [21]) and on verapamil and atenolol in INVEST (1.03; CI, 0.90–1.18; P = 0.68 [29]). Furthermore, in our previous [5,6] as well as our current analysis, ACE inhibitors and old drugs performed equally well in the prevention of myocardial infarction. ANBP2 [23,82] was the only actively controlled trial of ACE inhibitors, which showed a borderline significant benefit over conventional therapy in the prevention of fatal and nonfatal myocardial infarction (0.70; CI, 0.45–1.00; P = 0.048). Thus, in the actively controlled trials, new drugs and conventional therapy prevented coronary complications to the same extent. This conclusion is supported by the observation that for myocardial infarction none of the P-values for heterogeneity reached statistical significance.

Among eight placebo-controlled secondary prevention studies [41,48,49,51, 54,55,57,58], ACE inhibitors reduced the risk of myocardial infarction by 20%. However, among individual trials, ACE inhibition did not lead to significantly

less myocardial infarcts in CAMELOT/En (0.55; CI, 0.26–1.15; $P = 0.11$ [41]), DIABHYCAR (0.79; CI, 0.57–1.10; $P = 0.16$ [54]) and PEACE (1.00; CI, 0.83–1.20; $P > 0.99$ [58]). Some investigators [58] attributed these null results to the high frequency of background therapy with lipid-lowering drugs and anti-platelet agents. However, this explanation is unlikely because the use of such drugs was similarly high in trials that demonstrated a difference in the risk of myocardial infarction, such as EUROPA [49], VALUE [39,40] or CAMELOT/Aml [41]. More likely explanations are that either the sample size was too small to achieve a significant result [41] or that the difference in systolic blood pressure between randomized groups was relatively small [54,58].

Among five placebo-controlled secondary prevention studies [35,41,43,44,47], dihydropyridine calcium-channel blockers did not significantly decrease the risk of myocardial infarction. However, across the three trials in which amlodipine was the experimental drug, including CAMELOT/Aml [41], IDNT2 [35], PREVENT [43], amlodipine was 31% ($P = 0.033$) better than placebo. These results are in line with those of the VALUE trial [39,40], in which amlodipine showed a 15% benefit vs. valsartan ($P = 0.02$). These observations raise the question whether for prevention of myocardial infarction all dihydropyridine calcium-channel blockers behave as a single class. Indeed, among individual trials, point estimates trended to be higher than unity or were equal to unity for nisoldipine vs. enalapril in the revised ABCD/HT results (3.30; CI, 1.50–7.10; $P = 0.029$ [64]); for nisoldipine vs. placebo in NICOLE (1.25; CI, 0.56–2.86; $P = 0.58$ [47]); for nifedipine vs. co-amilozide in INSIGHT [12] for fatal cases (3.22; CI, 1.18–8.80; $P = 0.017$) as well as for nonfatal infarcts (1.09; CI, 0.76–1.58; $P = 0.52$); for nifedipine vs. ACE inhibitors in JMIC-B (1.31; CI, 0.63–2.74; $P = 0.47$); and for nifedipine vs. placebo in ACTION (1.04; CI, 0.88–1.24; $P = 0.62$ [44]). Differences between randomized groups in achieved systolic blood pressure were small and nonsignificant in ABCD/HT [61] and INSIGHT [12], but favored the calcium-channel blocker in NICOLE (9.1 mmHg [47]), JMIC-B (2.0 mmHg [83]) and ACTION (6.0 mmHg [44]).

The results of the blood pressure lowering limb of ASCOT [84], due to be published in 2005, might shed more light on the prevention of myocardial infarction. In a 2×2 factorial design [84,85], 19 342 hypertensive patients were randomized to amlodipine combined or not with perindopril or to atenolol combined or not with bendrofluazide (open-label treatment with blinded endpoint validation), while a subgroup of 10 305 patients received double-blind treatment with either atorvastatin or placebo. The primary endpoint was the combination of death from coronary heart disease and nonfatal myocardial infarction [84,85]. Because of benefit, the atorvastatin and amlodipine arms stopped in September 2002 [85] and November 2004, respectively. Achieved blood pressure was lower on new vs. old antihypertensive drugs. An interaction between blood pressure and lipid lowering might therefore have contributed to the immediate separation of the Kaplan–Meier estimates in the lipid trial [85].

Prevention of heart failure

The risk of heart failure was higher on calcium-channel blockers than on conventional therapy without heterogeneity among the trials. In individual studies, the risk of heart failure was significantly increased on nifedipine GITS in INSIGHT (2.18; CI, 1.06–2.18; $P = 0.03$ [12]); on amlodipine in ALLHAT (1.38; CI, 1.25–1.50;

$P < 0.001$ [21]); and on verapamil in CONVINCE (odds ratio 1.30; CI, 1.00–1.69; $P = 0.05$ [19]). Calcium-channel blockers reduce left ventricular afterload. However, neuroendocrine activation in response to arterial vasodilatation, as for instance exemplified by the increase in heart rate on nifedipine in ACTION [44] as well as the direct negative inotropic action on the myocardium may elicit heart failure in predisposed patients [86]. Nevertheless, on top of diuretics and/or ACE inhibitors, long-acting dihydropyridines [87,88], diltiazem [89] and verapamil [90] can be used in patients with left ventricular dysfunction to lower blood pressure or to treat angina pectoris. The reduction of heart failure on nifedipine GITS vs. placebo in ACTION (0.71; CI, 0.54–0.94; $P = 0.015$ [44]) was unexpected, but might be due to the 6.0 mmHg lower systolic blood pressure in the patients on nifedipine or to unbalanced prescription of background medications in favor of the actively treated patients. The ACTION report [44], similarly to several other studies [54,55,58], did not provide any information on concomitant medications after randomization.

Among the trials of new vs. old drugs [7], all newer agents on average performed 23.1% worse in the prevention of heart failure than conventional therapy. This is not surprising because both diuretics and β–blockers belong to the standard of care for this condition [91]. The same is true for ACE inhibitors given on top of digitalis and diuretics. AR1 blockers, perhaps with the exception of candesartan titrated up to 32 mg daily [92–95], are only indicated as alternative to ACE inhibitors when class-specific side-effects, such as cough, occur [91,96–98]. Two trials of the combination of ACE inhibitors and AR1 blockers in patients with heart failure reported contradictory results [94,99].

The higher risk of heart failure on lisinopril in ALLHAT (1.19; CI, 1.07–1.31; $P < 0.001$ [21]) is contra-intuitive, whereas the results of the ALLHAT doxazosin arm (1.80; CI, 1.61–2.02; $P < 0.001$ [14,32]) were in line with previous studies [100]. In trials of ACE inhibitors in patients with heart failure [91] or high cardiovascular risk [51,55], these agents were always combined with diuretics. In contrast to current guidelines [3,101], in therapy-resistant ALLHAT patients, lisinopril had to be associated with sympatholytic agents and/or hydralazine before diuretics could be added [21]. Furthermore, heart failure in ALLHAT was only a component of a secondary endpoint, which did not lead to an increase in cardiovascular [21] or total [14,21] mortality. At randomization, 90.2% of the ALLHAT patients were already on antihypertensive drugs, diuretics in most cases. Thus, the patients allocated amlodipine, lisinopril or doxazosin were at risk of rapidly losing the protection of their previous diuretic treatment, whereas in those of the chlorthalidone group the volume-dependent signs and symptoms of heart failure remained suppressed. These design features of ALLHAT likely explain why the Kaplan–Meier estimates for heart failure separated immediately after randomization [14,21,32]. Because of the weight of ALLHAT in our overview, pooled estimates including this trial must be cautiously interpreted.

In the main analysis of the VALUE trial [39], the risk of heart failure was slightly less on valsartan than amlodipine (0.89; CI, 0.77–1.03; $P = 0.12$). This trend reached borderline significance in two post-hoc analyses [39,40]. First, the VALUE investigators artificially subdivided the follow-up period into consecutive intervals characterized by progressively decreasing between-group differences in systolic blood pressure [39]. In the interval from 36 to 48 months the risk was 0.69 (CI, 0.51–0.94). However, these time-interval specific analyses were biased for all periods but the first 0–3 months, because event rates in each

sequential period were conditional on those occurring earlier [39,40]. Patients continuing to each subsequent period were therefore unbalanced with regard to risk and randomization. Second, in an accompanying paper [40], the VALUE consortium performed serial median matching using the systolic blood pressure level at 6 months and found that the risk of heart failure on valsartan vs. amlodipine was 0.81(CI, 0.66–0.99; $P = 0.04$). This matched-pair approach [40] accounted for the attained systolic pressure (within 2 mmHg) and other cardiovascular risk factors, but excluded 5233 patients (34.3%) whose systolic pressure was too high on valsartan or too low on amlodipine to allow matching.

CONCLUSIONS

Most trials published over the past decade mainly enrolled middle-aged and older patients of male sex at high cardiovascular risk who had previous complications, associated diseases or both. To what extent their findings can be reasonably extrapolated to younger and female patients in a routine clinical setting remains a matter of concern [102].

This overview suggested that dihydropyridine calcium-channel blockers might offer a selective benefit in the prevention of stroke and inhibitors of the renin–angiotensin system in the prevention of heart failure, resulting in a similar overall protection against cardiovascular complications. This is in contrast to some individual studies showing greater [55,56] or reduced [14,32] cardiovascular benefit in patients treated with newer drugs as compared with conventional antihypertensive therapy. However, outcome results should never be interpreted without taking into account differences in achieved blood pressure between randomized groups. In Chapter 30, we will investigate to what extent blood pressure reduction accounts for results of individual outcome trials.

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ACRONYMS OF TRIALS

AASK (the African American Study of Kidney disease and hypertension [31,60,76,77]); **ABCD** (Appropriate Blood Pressure Control in Diabetes trial [61–65]); **ABCD/HT** (Appropriate Blood Pressure Control in Diabetes trial – nisoldipine vs. enalapril in hypertensive patients [61,63,64]); **ABCD/NT** (Appropriate Blood Pressure Control in Diabetes trial – tight vs. usual blood pressure control in normotensive hypertensive patients [65]); **ACTION** (A Coronary disease Trial Investigating Outcome with Nifedipine GITS [44,45]); **ALLHAT** (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart

Attack Trial [21]); **ALLHAT/Aml** (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – amlodipine vs. chlorthalidone [21]); **ALLHAT/Dox** (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – doxazosin vs. chlorthalidone [14,32]); **ALLHAT/Lis** (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial – lisinopril vs. chlorthalidone [21]); **ANBP2** (Australian comparative outcome trial of angiotensin-converting enzyme inhibitor- and diuretic-based treatment of hypertension in the elderly [23]); **ASCOT** (the Anglo-Scandinavian Cardiac Outcomes Trial [84,85]); **ATMH** (Australian Trial in Mild Hypertension [103]); **BENEDICT** (BErgamo NEphrologic DIabetes Complications Trial [66,67]); **CAMELOT** (Comparison of AMlodipine vs. Enalapril to Limit Occurrences of Thrombosis [41]); **CAMELOT/Aml** (Comparison of AMlodipine vs. Enalapril to Limit Occurrences of Thrombosis – amlodipine vs. placebo [41]); **CAMELOT/En** (Comparison of AMlodipine vs. Enalapril to Limit Occurrences of Thrombosis – enalapril vs. placebo [41]); **CASTEL** (CArdiovascular STudy in the ELderly [104]); **CALM** (CAndesartan and Lisinopril Microalbuminuria study [68]); **CONVINCE** (Controlled Onset Verapamil Investigation of Cardiovascular Endpoints Trial [19]); **CAPPP** (Captopril Prevention Project [9,105]); **CONVINCE** (Controlled Onset Verapamil Investigation of Cardiovascular Endpoints Trial [19]); **DIABHYCAR** (the noninsulin-dependent DIAbetes, HYpertension, microalbuminuria or proteinuria, CArdiovascular events, and Ramipril study [52–54]); **ELSA** (European Lacidipine Study on Atherosclerosis [20,22]); **EUROPA** (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease [49]); **EWPHE** (trial conducted by the European Working Party on High Blood Pressure in the Elderly [106,107]); **HEP** (trial of Hypertension in Elderly Patients in primary care [108]); **HDFP** (Hypertension Detection and Follow-Up Program [109,110]); **HOPE** (Heart Outcomes Prevention Evaluation Study [55,56]); **HOT** (Hypertension Optimal Treatment trial [111]); **HOT/LH** (Hypertension Optimal Treatment trial [111] – 80 vs. 90 mmHg as target diastolic pressure); **HOT/MH** (Hypertension Optimal Treatment trial [111] – 85 vs. 90 mmHg as target diastolic pressure); **HYVET** (HYpertension in the Very Elderly Trial pilot trial [25]); **HYVET/AD** (HYpertension in the Very Elderly Trial pilot trial – ACE inhibition vs. diuretic treatment [25]); **HYVET/BP** (HYpertension in the Very Elderly Trial pilot trial – blood pressure lowering drugs vs. no treatment [25]); **IDNT2** (Irbesartan Diabetic Nephropathy Trial in patients with type-2 diabetes mellitus [33–35]); **INSIGHT** (International Nifedipine GITS Study – Intervention as a Goal for Hypertension Therapy [12,112]); **IRMA2** (Irbesartan in patients with type-2 diabetes and MicroAlbuminuria study[69]); **INVEST** (INternational VErapamil SR/trandolapril STudy [29]); **JMIC-B** (the Japan Multicenter Investigation for Cardiovascular diseases-B [83]); **LIFE** (Losartan Intervention For Endpoint Reduction in hypertension study [17,18,113,114]); **LIFE/All** (Losartan Intervention For Endpoint Reduction in hypertension study – all patients [18]); **LIFE/DM** (Losartan Intervention For Endpoint Reduction in hypertension study – diabetic subgroup [17]); **HSCS** (Hypertension-Stroke Cooperative Study [115]); **MIDAS** (Multicenter Isradipine Diuretic Atherosclerosis Study [8]); **MIDAS/NICS/VHAS** (combined results of MIDAS, [8] NICS [10] and VHAS [15]); **MRC1** (Medical Research Council trial of treatment of mild hypertension [116]); **MRC2** (Medical Research Council trial of treatment of hypertension in older adults [117]); **NICOLE** (NIsoldipine in COronary artery disease in

LEuven [46,47]); **NICS** (National Intervention Cooperative Study in Elderly Hypertensives [10]); **NORDIL** (Nordic Diltiazem Study [13]); **OSLO** (Oslo Study on the Treatment of Mild Hypertension [27]); **PART2** (Prevention of Atherosclerosis with Ramipril Trial [57]); **PART2/SCAT** (combined results of PART2 [57] and SCAT [48]); **PATS** (Post-stroke Antihypertensive Treatment Study [80]); **PEACE** (Prevention of Events with Angiotensin Converting Enzyme inhibition [58]); **PREVENT** (Prospective Randomized Evaluation of the Vascular Effects Norvasc Trial [42,43]); **PROGRESS** (Perindopril PrOtection Against Recurrent Stroke Study [51,59,118]); **PROGRESS/Com** (Perindopril PrOtection Against Recurrent Stroke Study [51,59,118] – group on combined therapy); **PROGRESS/Per** (Perindopril PrOtection Against Recurrent Stroke Study [51,59,118] – group on single-drug treatment); **REIN** (Ramipril Efficacy In Nephropathy trial [70]); **RENAAL** (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [71]); **RCT70-80** (combined results of 4 smaller trials published from 1970 through 1980, including HSCS, [115] OSLO, [27] USPHS, [119] and VACS [120]); **SCAT** (Simvastatin/Enalapril Coronary Atherosclerosis Trial [48]); **SCOPE** (Study on COgnition and Prognosis in the Elderly [24,121,122]); **SHELL** (Systolic Hypertension in the Elderly Long-term Lacidipine trial [30]); **SHEP** (Systolic Hypertension in the Elderly Program [123,124]); **STONE** (Shanghai Trial of Nifedipine in the Elderly [125]); **STOP1** (Swedish Trial in Old Patients with hypertension [126]); **STOP2** (Swedish Trial in Old Patients with hypertension–2 [11]); **STOP2/ACEIs** (angiotensin-converting enzyme inhibitor arm of STOP2 [11]); **STOP2/CCBs** (calcium-channel blocker arm of STOP2 [11]); **Syst-China** (Systolic Hypertension in China trial [127,128]); **Syst-Eur** (Systolic Hypertension in Europe trial [129–131]); **TEST** (Tenormin after Stroke and TIA [79]); **UKPDS** (UKPDS Hypertension in Diabetes Study [16,132]); **UKPDS/CA** (UKPDS Hypertension in Diabetes Study – captopril vs. atenolol [16]); **UKPDS/LH** (UKPDS Hypertension in Diabetes Study – low vs. high on-treatment blood pressure [132]); **USPHS** (United States Public Health Service Hospitals Cooperative Study [119]); **VACS** (Veterans Administration Cooperative Study in patients with diastolic blood pressure averaging 90–114 mmHg [120]); **VALUE** (Valsartan Antihypertensive Long-term Use Evaluation [36–40]); **VHAS** (Verapamil in Hypertension and Atherosclerosis Study [26])

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